REMARKS

Applicant herewith submits a Request for Continued Examination in the above-identified patent application that had been subject to final rejection.

This Request for Continued Examination (RCE) is filed under 37 C.F.R. § 1.114. This RCE is being filed prior to the abandonment of the application, as the period for response to the Office Action has been extended until December 12, 2007 by the filing of a request for a two-month extension of time under 37 C.F.R. § 1.136(a) and the appropriate fee for this request for extension of time. A fee of $60.00 (small entity) for a one-month extension of time was submitted with the previously filed amendment on October 29, 2007. Accordingly, the balance of $170.00 for the fee due for the two-month extension of time for a small entity is paid herewith.

The amendments to the claims that have not been previously entered and the arguments regarding patentability applicable to the claims as amended constitute the submission required for an RCE under 37 C.F.R. § 1.114(c). The fee for a RCE under 37 C.F.R. § 1.17(e) of $405.00 (small entity) accompanies this RCE.

Therefore, this Request for Continued Examination is properly submitted, and the finality of the Office Action of July 12, 2007 should therefore be withdrawn.

Claims 10-19 are pending in the above-identified patent application, claims 1-9 having been cancelled by this amendment. Accordingly, claims 10-19 remain for consideration in the above-identified patent application.

Claims 10-19 were rejected in the previous final Office Action under the first paragraph of 35 U.S.C. § 112, allegedly for failing to comply with the written description requirement. These rejections are addressed below. By addressing these rejections, Applicant does not acquiesce in a determination that these rejections were proper or should be applied to the claims as amended.

Claims 10-19 were also rejected in the previous final Office Action under the first paragraph of 35 U.S.C. § 112, allegedly for failing to comply with the enablement requirement. These rejections are also addressed below. By addressing these rejections, Applicant again does not acquiesce in a determination that these rejections were proper or should be applied to the claims as amended.

Reexamination of the application as amended, reconsideration of the rejections, and allowance of the claims remaining for consideration are respectfully requested.

The shortened statutory period for response expires on December 12, 2007, having been extended by a two-month Request for Extension of Time filed under 37 C.F.R. § 1.136(a). Accordingly, this response is being filed in a timely manner.

I. AMENDMENTS TO THE APPLICATION

Entry of the amendments to the application is respectfully requested. As detailed below, these amendments introduce no new matter.

Claims 1-9, previously withdrawn, are cancelled. This cancellation is without prejudice to the filing by Applicants of a properly copending divisional, continuation, or continuation-in-part application directed to the subject matter of any or all of these claims.

The amendments to claim 10 are supported by the specification, specifically at page 4, lines 5-9 of the original specification, at page 15, lines 1-12 of the original specification, and by originally filed Figure 5.

The language in claim 10 that the chimeric isoprenoid synthase polypeptide catalyzes "the production of at least one isoprenoid reaction product that is not produced in the absence of the second isoprenoid synthase polypeptide" is supported by the specification at page 4, lines 5-9 of the original specification. The specification clearly and unequivocally states that the chimeric isoprenoid synthase is "capable of catalyzing the production of isoprenoid reaction products that are not produced in the absence of the second domain of the second, heterologous isoprenoid synthase. Given how these domains are joined in the chimeric isoprenoid synthase, this language clearly provides support for this portion of the amendment to claim 10.

The language in claim 10 that the chimeric isoprenoid synthase polypeptide catalyzes "the production of more than one isoprenoid reaction product in a ratio differing from the ratio of the products produced in the absence of the second isoprenoid polypeptide" is supported by the specification at page 15, lines 1-12, describing the ratio-determinant domain, and also in Figure 5. These portions of the specification make it clear to one of ordinary skill in the art that the function of this ratio-determinant domain is to regulate the ratio of the production of two or more isoprenoid reaction products. For example, the reaction products resulting from expression of constructs CH4, CH10, CH11, and CH12 were generated in a ratio of from about 60%-70% TEAS-specific products to about 30%-40% HVS-specific products. By contrast, an inverse ratio of reaction products resulted from expression of the constructs CH13 and CH14. These results, also depicted in Figure 5, makes it clear that a specific region of the constructs of the present invention, namely the region encompassed by the *Xba*I to *Hinc*II domain, influenced the relative ratio of reaction products, and changing this region led to a change in the ratio. This language therefore clearly provides support for this portion of the amendments to claim 10.

Accordingly, entry of the amendments is respectfully requested.

This response is being filed in accordance with recently revised 37 C.F.R. § 1.121, as set forth in 68 F.R. 38611 (June 30, 2003). If the amendment is considered to

not be in compliance with recently revised 37 C.F.R. § 1.121, the Examiner is respectfully requested to contact the undersigned at his earliest possible convenience.

II. THE REJECTIONS UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112

A. The Rejections of Claims 10-19 for Lack of Compliance with the Written Description Requirement

Claims 10-19 were rejected in the prior final Office Action under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the written description requirement.

Specifically, the Office Action stated that Applicant did not describe the broadly claimed genus of chimeric isoprenoid synthases that are comprised of a first isoprenoid synthase and a second and different isoprenoid synthase "in their entirety or in portions thereof." (The quoted language, from page of the Office Action, is referred to below with respect to the actual language of the rejected claims.) The Office Action further stated that Applicant only described activity in chimeric isoprenoid synthases CH4 and CH10-CH14 comprising portions of isoprenoid synthases TEAS (tobacco aristolochene synthase and HVS (henbane vetispiradiene synthase). The Office Action further stated that Applicant did not describe the products formed by the undisclosed recombined isoprenoid synthases or chimeric isoprenoid synthases. According to the Office Action, Applicant has not provided a structure-function relationship for isoprenoid synthases other than the isoprenoid synthases comprising portions of isoprenoid synthases TEAS (tobacco aristolochene synthase and HVS (henbane vetispiradiene synthase).

The Office Action concluded that, based upon the disclosure of TEAS and HVS, there was insufficient identifying characteristics to allow one skilled in the art to completely determine the structure of the broadly claimed chimeric isoprenoid synthases,

absent further guidance. The Office Action stated that the claimed genus encompassed undisclosed or yet to be discovered sequences, the disclosure of TEAS and HVS chimeric variants CH4 and CH10-CH14 does not provide adequate description of the broadly claimed genus.

As detailed below, this rejection is respectfully traversed as applied to the amended claims. The specification is sufficiently detailed to meet the written description requirement under the first paragraph of 35 U.S.C. § 112.

The general standard for compliance with the written description requirement has been established by case law such as In re Edwards, 196 U.S.P.Q. 465 (C.C.P.A. 1978). In In re Edwards, the Court of Customs and Patent Appeals articulated the function of the written description requirement in the following language:

> [The f]unction of [the] written description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; to comply with the description requirement, it is not necessary that the application describe the claimed invention in ipsis verbis; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him.

Id. at 567 (citations omitted). See also Vas-Cath, Inc. v. Mahurkar, 19 U.S.P.Q. 2d 1111 (Fed. Cir. 1991) (to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed).

In order to satisfy the written description requirement, it is sufficient that the specification "convey clearly to those skilled in the art the information that the

applicant has invented the specific subject matter later claimed." In re Wertheim, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). Additionally, the United States Patent and Trademark Office always has the burden of demonstrating that the applicant has failed to comply with the written description requirement. In re Salem, 193 U.S.P.Q. 513, 518 (C.C.P.A. 1987).

Again, all that is required to satisfy the written description requirement of the first paragraph of 35 U.S.C. § 112 is that the patent specification describes the claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed subject matter, to ensure, e.g., that the invention had possession of the claimed subject matter as of the desired priority date. Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997). In the context of nucleic acids, and by analogy, in the context of proteins encoded by nucleic acids, the recitation of structure for the claimed subject matter need not be great in order to satisfy the written description requirement. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of a genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Regents of the University of California, 43 U.S.P.Q. 2d at 1406. Moreover, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in the application by "other appropriate language." Id.

This basic standard for compliance with the written description requirement under the first paragraph of 35 U.S.C. § 112 is satisfied by the insertion of specific language into the claims reciting the domains involved in the chimeric proteins encoded by these DNA constructs, together with the activity of the resulting chimeric proteins. There are sufficient relevant identifying characteristics to meet this standard as applied to the amended claims.

Once an amino acid sequence is selected, all nucleotide sequences encoding that amino acid sequence comply with the written description requirement,

because one of ordinary skill in the art can rapidly determine all corresponding nucleotide sequences. This is because the genetic code is invariant, and the codons corresponding to each amino acid are known and readily determinable by one of ordinary skill in the art. The situation is analogous to the possible rejections under the first paragraph of 35 U.S.C. § 112 for lack of enablement in this context, as considered in In re Deuel, 34 U.S.P.Q. 2d 1210, 1215 (Fed. Cir. 1995). Therefore, if sufficient detail is provided in the specification regarding the amino acid sequence of the chimeric protein, there can be no issue regarding the presence of sufficient support for nucleic acid molecules encoding the chimeric protein under the written description requirement of the first paragraph of 35 U.S.C. § 112.

With respect to the claims subject to this rejection, there is sufficient structural and functional detail to meet the standards of the written description requirement of the first paragraph of 35 U.S.C. § 112. As clearly established above, both structural and functional limitations can be considered in determining whether the specification meets the standards of the written description requirement of the first paragraph of 35 U.S.C. § 112. There is no requirement that the entire sequence of either a polynucleotide or polypeptide be recited in the specification to meet the standards of the written description requirement of the first paragraph of 35 U.S.C. § 112. Moreover, as detailed below, the functional language of the claims need also to be considered with respect to the compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112.

The "Guidelines for Examination of Patent Examinations Under the 35 USC § 112 para. 1 'Written Description' Requirement," 66 Fed. Reg. 1099 (January 5, 2001) issued by the United States Patent and Trademark Office, state that the policy goals of the written description requirement are to: (i) clearly convey to the public what was invented; (ii) put the public in possession of what the applicant claims as the invention; and (iii) prevent an applicant from claiming subject matter that was not described in the specification as filed. These policy requirements are met by the amended claims.

Moreover, possession of the claimed invention can be shown by any of: (1) actual reduction to practice; (2) a "clear depiction" of the invention in detailed drawings; or (3) a description of sufficient relevant identifying characteristics. These guidelines are stated in the alternative, so that all three requirements are not required. Only one of these requirements is necessary to satisfy the standard for written description under the first paragraph of 35 U.S.C. § 112.

Again, all that is required to satisfy the written description requirement of the first paragraph of 35 U.S.C. § 112 is that the patent specification describes the claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed subject matter, to ensure, e.g., that the invention had possession of the claimed subject matter as of the desired priority date. Regents of the University of California v. Eli Lilly & Co., 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997). In the context of nucleic acids, and by analogy, in the context of proteins encoded by nucleic acids, the recitation of structure for the claimed subject matter need not be great in order to satisfy the written description requirement. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of a genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Regents of the University of California, 43 U.S.P.Q. 2d at 1406. Moreover, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in the application by "other appropriate language." Id. As detailed below, the functional language is within the category of "other appropriate language" such that the test of Regents of the University of California is satisfied. This functional language includes language identifying the partial reactions carried out by the two domains identified, and how those partial reactions are interrelated to produce the final product.

Moreover, possession of the claimed invention can be shown by any of: (1) actual reduction to practice; (2) a "clear depiction" of the invention in detailed drawings; or (3) a description of sufficient relevant identifying characteristics. These

guidelines are stated in the alternative, so that all three requirements are not required. Only one of these requirements is necessary to satisfy the standard for written description under the first paragraph of 35 U.S.C. § 112. There is actual reduction to practice in terms of the production of several active chimeric synthase molecules, as set forth in Figure 4B. The actual reduction to practice goes beyond one specific embodiment. In fact, a significant number of chimeric proteins were shown to exist and be active in Figure 4B. The results recited in the specification indicate that a considerable amount of domain exchange can be performed and is consistent with the enzymatic activity of the chimeric synthases of the invention. This is shown, for example, in Figure 4B. The results shown in Figure 4B are analyzed in detail below. There is no basis for the argument that this disclosure is insufficient to provide sufficient relevant identifying characteristics, as a considerable degree of structural information is provided, not merely functional information. This structural information is implied by the organization of these chimeric proteins into domains, and the activity of the domains that is associated with specific partial enzymatic reactions.

Moreover, it is well-established that an applicant need not disclose every species encompassed by a claim. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976). The written description requirement cannot force such a requirement, which would be unreasonable. Patents are not production documents.

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. In re Wertheim, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims").

This argument is supported by other results on domain swapping. These results indicate what domains are responsible for particular steps in the enzymatic synthesis of terpenes. These domains are associated with both structural and functional features in the DNA and are correlated with the amino acid sequences encoded by

particular exons in the DNA. This is in accord with the generally-accepted understanding about the significance of protein domains.

It is well understood that, in complex proteins, discrete domains are conserved evolutionary and are associated both with specific structural features and with specific functions. Such domains can be identified and manipulated based on both structural and functional information. See J.-R. Garel, "Folding of Large Proteins: Multidomain and Multisubunit Proteins" in Protein Folding (T.E. Creighton, ed., W.H. Freeman & Co., New York, 1992), pp. 406-407, accompanying this Request for Continued Examination as Exhibit A. This illustrates the understanding of domains and how they can be used to understand protein structure and allow manipulation of multi-domain proteins while preserving the functions associated with each domain. In general, a domain is a part of the polypeptide chain of a protein molecule that forms a compact globular substructure with more interactions within itself than with other parts of the polypeptide chain. These domains not only have a compact substructure in and of themselves, but they typically carry out a partial activity or a portion of a reaction catalyzed by the protein as an enzyme. Typically, the stability of such a domain toward a denaturant such as heat, guanidinium ions, or urea is not markedly modified by the presence of the rest of the protein. This leads to the idea that domains can be duplicated or exchanged between proteins to build proteins with different functions, such as the catalysis of different enzymatic reactions, with the maintenance of the structural and functional integrity of the domains. This idea is employed in designing the constructs that encode the chimeric isoprenoid synthases incorporated in plant cells or transgenic plants in the present invention.

In many cases, the domains are contiguous or nearly contiguous with exons in a protein where the gene encoding the protein has multiple exons interrupted by non-expressed introns. This suggests that the proteins evolved by adding exons that encoded amino acid sequences having particular functions. The correspondence between exons and functional or structural domains is also employed in designing the constructs

that encode the chimeric isoprenoid synthases incorporated in plant cells or transgenic plants in the present invention.

Thus, the recitation of these domains provides both structural and functional information about the claimed chimeric isoprenoid synthases. This structural and functional information is sufficient to provide a written description of the claimed invention.

In general, the work of Applicant establishes that chimeric isoprenoid synthases that catalyze a spectrum of reaction products not obtained with naturally occurring wild-type isoprenoid synthases can be obtained. These chimeric synthases are obtained by ligating conserved functional domains of different isoprenoid synthases together, resulting in synthases that can catalyze more than one reaction in isoprenoid synthesis.

Isoprenoid synthase genes are found in a large variety of organisms including bacteria, plants, and fungi. In general, isoprenoid synthase genes, and the proteins encoded by them, demonstrate highly conserved and distinct domain regions. The individual members of the isoprenoid synthase families are multi-domain proteins that catalyze the synthesis of particular biologically active chemical compounds with a wide variety of functional groups. For any particular family member, different protein domains catalyze different steps in the overall synthesis reaction. Each family member catalyzes the synthesis of a different terpenoid compound because each member contains a different collection or arrangement of protein functional domains.

This analysis has been applied to the isoprenoid synthases. Swapping regions of the proteins that are contiguous or nearly contiguous between different isoprenoid synthases has led to the identification of functional domains responsible for the terminal enzymatic steps that catalyze the last step in the formation of specific terpenes. For example, work performed on the 5-epi-aristolochene synthase (TEAS) from *Nicotiana tabacum* (the tobacco plant) and the *Hyoscyamus muticus* (the henbane

plant) vetispiradiene synthase (HVS) revealed that exon 4 of TEAS and exon 6 of HVS, respectively, were responsible for the reaction product specificity of the synthases. Combining these functional domains resulted in novel enzymes capable of synthesizing new reaction products, as shown in U.S. Patent No. 5,824,774. The above-identified pending application is a continuation of Application Serial No. 09/576,057, which in turn is a continuation of Application Serial No. 09/514,513, which in turn is a divisional of Application Serial No. 09/134,699, which in turn was is a continuation of Application Serial No. 08/631,341, on which U.S. Patent No. 5,824,774. Therefore, the disclosure of U.S. Patent No. 5,824,774, which disclosed that it was possible to combine these functional domains to produce novel recombinant synthase enzymes, also supports the argument that both the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112 are complied with in the above-identified pending application.

Work subsequent to the filing date of this application demonstrates that these enzymes contain conserved domains that can be reorganized in protein molecules to provide novel chimeric enzymes. The process by which these conserved domains are reorganized is known as domain swapping and is well known in the art. The process of domain swapping substantially preserves the structural and functional integrity of the domains involved in it. For example, in M. Schalk & R. Croteau, "A Single Amino Acid Substitution (F363I) Converts the Regiochemistry of the Spearmint (-)-Limonene Hydroxylase from a C6- to a C3-Hydroxylase," Proc. Natl. Acad. Sci. 11948-11953 (2000) ("Schalk & Croteau (2000))," accompanying this RCE as Exhibit B, chimeric hydroxylases were generated using a domain-swapping process. This is completely consistent with what was known prior to that date about the function of domains in proteins and the ability to interchange domains while retaining the function of each domain.

Thus, it is evident from the studies of Applicant and from other work that it was known that isoprenoid synthase genes contained several highly conserved domain regions, and that domain swapping could be practiced on such genes. This work

establishes that Applicant had possession of the claimed invention at the time of filing the above-identified patent application and that one of ordinary skill in the art would recognize what is claimed was in possession of the inventors. That is all that is required to meet the written description requirement of the first paragraph of 35 U.S.C. § 112.

This is clearly not a situation in which a biomolecule sequence is described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence. Here there is a disclosed correlation between the functions of the domains and the structure of the sequence. See M.P.E.P. § 2163.

The results of Figure 4A and 4B are particularly relevant with respect to compliance with the written description requirement. The specification, at page 12, line 15, to page 14, line 9, states as follows:

> As shown in Figs. 4A-B, the dominant reaction product resulting from the expression of the tobacco TEAS gene expressed was 5-epi-aristolochene, and vetispiradiene was found to be the dominant reaction product resulting from the expression of the HVS gene. The predominant reaction products generated by the expression of CH1 and CH2 were also HVS-specific (i.e., vetispiradiene), with enzyme specific activities similar to those found for HVS that was expressed from the pBSK-HVS plasmid. These results indicated that the amino-terminal half of TEAS and HVS were functionally equivalent with respect to the HVS carboxy-terminus and do not contribute to the specificity of the reaction product. CH7, having an HVS amino terminus and a TEAS carboxy terminus, is the converse construct of CH2, and the resulting synthase activity was expected to result in expression of a TEAS-specific product (i.e., 5-epiaristolochene). Immunodetection assays revealed that synthase protein produced upon expression of CH7 was found to be of the correct size and expected abundance (data not shown); however, no enzyme

activity was detected. The lack of enzyme activity indicated that interactions between the carboxy and amino terminal portions of the protein contributed to enzyme activity. This interpretation is further supported by comparing the specific activity of the enzymes generated by the expression of the CH5 and CH6 constructs. CH5 resulted in the expression of a product having a 10-fold lower specific activity of synthase enzyme activity than the other chimeric synthases, even though the absolute level of expressed protein was similar to the other constructs (as determined by immunodetection, data not shown). Substituting an HVS carboxy-terminal region was found to restore the specific activity to the synthase enzyme that was generated by CH6.

Comparison of CH2 and CH3 chimeric synthases provided evidence for specificity of end-product formation residing within a domain of approximately 181 amino acids, corresponding to the NdeI and ClaI restriction sites within the TEAS and HVS genes. Expression of CH4 unexpectedly resulted in the production of a chimeric synthase protein capable of generating reaction products reflective of both the TEAS and HVS enzymes. We interpreted this result to indicate that amino acids 261 to 379 within the tobacco 5-aristolochene synthase are responsible for the TEAS-specific products (i.e., the region corresponding to the *Nde*I to *Hinc*II fragment of the cDNA), while amino acids 379 to 442 within the *Hyoscyamus* protein are responsible for the HVS-specific products (i.e, the region corresponding to the *Hinc*II to *Cla*I fragment of the cDNA).

Our interpretation was confirmed by evaluating the expression products of CH11 and CH12. CH11 represented the substitution of the *Nde*I to *Hinc*II fragment of the *Hyoscyamus* gene with the corresponding tobacco gene fragment, and resulted in the production of an enzyme having HVS- and TEAS-specificity. CH12 represented a substitution of the *Hinc*II to *Cla*I fragment of the tobacco gene with the

corresponding *Hyoscyamus* gene fragment, and resulted in the production of an enzyme having HVS- and TEAS- specificity. Comparing CH11 to CH13 provided a further refinement in the domain characterization of the tobacco enzyme responsible for the TEAS-specific products. The fact that CH13 was found to be a multifunctional enzyme indicated that the 81 amino acids encoded by the DNA fragment residing between the *Nde*I to *Xba*I restriction sites of the tobacco cDNA were sufficient for formation of the predominant TEAS specific products. This interpretation was confirmed by substituting the domain contained within the *NdeI/Xba*I HVS cDNA restriction fragment of CH14 with that of the TEAS gene (Fig, 4a).

Also extremely relevant is the information conveyed to one of ordinary skill in the art by Figure 5 of the above-identified application. Figure 5 is a schematic illustration showing the correspondence between exons and functional domains within isoprenoid synthases. The organization of exons within the TEAS gene is virtually identical to that of the HVS and casbene synthase genes (Fig. 5, upper diagram). The lower diagram of Figure 5 shows the alignment of functional domains to the exonic organization of the TEAS and HVS genes. The lower diagram shows that specific domains are associated with the production of 5-epi-aristolochene and vetispiradiene. An additional domain is also associated with the ratio of these products. Finally, a large portion of the amino-terminal region of these enzymes are common to at least both of the TEAS and HVS genes.

Therefore, one of ordinary skill in the art would reach the following conclusions from the data presented in the above-identified application:

(1) Specific sequences or domains are responsible for the production of the final TEAS-specific or HVS-specific products, namely 5-epi-aristolochene and vetispiradiene, respectively, and these sequences or domains have been identified and can

be transferred from one protein to another to generate chimeric proteins having the desired specificity.

(2) Transferring or swapping the domains preserves their activity, thereby allowing one to construct the desired chimeric proteins.

(3) Multifunctional enzymes can be constructed by assembling the appropriate domains in the relationship shown in Figure 5.

(4) The domains correspond to exons found in the naturally-occurring genes, further strengthening the argument that the domains correspond to functional units in the naturally-occurring enzymes.

The identification of these domains, therefore, provides sufficient structural detail. This structural detail, considered together with the functional information provided and the correlation between structure and function, provides sufficient information for one of ordinary skill in the art to conclude that the inventor had possession of the claimed invention as of the filing date.

This conclusion is further supported by the results of site-directed mutagenesis, at page 15, line 14, to page 16, line 11, including Table I. These results establish that particular residues are responsible for the activity of these chimeric proteins. These residues include the DDXXD motif, and in particular the first aspartic acid residue within that motif. This further supports the structure-activity relationship that underlies the written description support present in the specification of this application.

The comment in the Office Action regarding the claims being directed to chimeric isoprenoid synthases "in their entirety or in portions thereof" is incomplete with respect to the actual scope of the claims. The claims are not directed to arbitrary portions of chimeric isoprenoid synthases in the sense that functional characteristics of the

portions are not considered. This is true even though there does not necessarily have to be a direct, one-to-one, correspondence between swapped domains and functional domains in terms of the manipulations that lead to the nucleotide sequences encoding the chimeric synthases of the present invention. Rather, the "portions" referred to are domains that may be present in the organization of naturally-occurring isoprenoid synthases. This does not exclude the use of domains comprised of random isoprenoid synthase gene segments or portions of sequences as used in gene shuffling to produce nucleotide sequences encoding chimeric synthases of the present invention, such as by techniques involving random fragmentation and recombination.

Additionally, the comment in the Office Action regarding the lack of description of the products is not germane to a written description rejection. This is true even though, as detailed below with respect to the rejection under the first paragraph of 35 U.S.C. § 112 for lack of enablement, there is in fact sufficient predictability in the reactions carried out by chimeric synthases encoded by nucleotide sequences according to the present invention to enable one of ordinary skill in the art to make and use the claimed invention. The pending claims are not directed to the products produced by the enzymatic reaction carried out by the chimeric isoprenoid synthase or to a method for generating such products. The claims are directed to nucleic acid constructs and cells incorporating such constructs, either directly or by way of vectors. The lack of description of the products, even if true, would have no bearing on the issue of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112 for these claims, which, again, are directed to nucleic acid constructs or cells incorporating them. Such description would not enable one of ordinary skill in the art to predict the required nucleic acid sequences, because even if it were possible to somehow ascertain the protein sequence of the enzyme from the product, an impossible task, the protein sequence would correspond to a large number of nucleotide sequences because of the degeneracy of the genetic code. Therefore, the lack of a description of the products, even if true, would have no relevance to the issue of compliance with the written description requirement of the first paragraph of 35 U.S.C. § 112 for these claims.

Despite that, the products, namely mixtures, in varying proportions, of 5-epi-aristolochene and vetispiradiene, are in fact described in the specification.

The Examiner, therefore, is respectfully requested to withdraw this rejection.

B. The Rejections of Claims 10-19 for Lack of Compliance with the Enablement Requirement

Claims 10-19 were also rejected under the first paragraph of 35 U.S.C. § 112 for lack of compliance with the enablement requirement.

The Office Action stated that Applicant's claims are not drawn to any particular reaction products, and that, since Applicant has not taught what products one could expect from the myriad of possible combinations of the broadly claimed chimeric isoprenoid synthases, Applicant has not taught how to make and use the invention as broadly claimed. The Office Action further stated that Applicant asserts that the present invention does not claim effectiveness of a chimeric isoprenoid synthase, but rather the DNA encoding a chimeric isoprenoid synthase. This point is addressed below with respect to the response to the rejection. Finally, the Office Action stated that Applicant has not taught the synthesis of "any novel isoprenoid compounds," and since Applicant has not claimed or taught the effect or result of the broadly claimed invention, Applicant has not taught how to make or use the invention as broadly claimed. The statement that Applicant has not taught the synthesis of "any novel isoprenoid compounds" is addressed below.

As detailed below, this rejection is respectfully traversed as applied to the amended claims.

Firstly, the burden of the United States Patent and Trademark Office has not been met for this rejection. This is because the statements in the Office Action do not

counter the actual examples and results cited in the specification. In particular, the specification provides, in Figure 4, the generation of chimeric isoprenoid synthases, and a rational basis for the prediction of the activity of such chimeric isoprenoid synthases. The results shown in Figure 4 are from an actual working example, the generation of the chimeric constructs CH1-CH14. The specification further provides specific amino acid residues that play a role in catalysis, and the result of modifying those amino acid residues. This provides the basis for a structure-activity relationship that enables one of skill in the art to identify invariant residues in the domains that comprise these chimeric isoprenoid synthases. As detailed below in connection with the elucidation of the factors set forth in In re Wands, U.S.P.Q. 2d 1400 (Fed. Cir. 1988), these results are extremely useful in reducing the likelihood of unpredictability in the results and reducing the degree of experimentation required.

It is established law with respect to enablement that the specification must be taken as being in compliance with the first paragraph of 35 U.S.C. § 112 unless there is reason to doubt the objective role of the statements contained in the specification which must be relied upon for enabling support. In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971).

Moreover, properly reasoned and supported statements explaining any failure to comply with the enablement requirements of 35 U.S.C. § 112 are a requirement to properly support such a rejection. The absence of such properly reasoned and supported statements compels withdrawal of this rejection. In re Wright, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993).

See also United States v. Telectronics, Inc., 8 U.S.P.Q. 2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc.,

231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom. Massachusetts Institute of Technology v. A.B. Fortia, 227 U.S.P.Q. 428 (Fed. Cir. 1985). See also In re Wands, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). This test is particularly applicable in complex technologies where absolute predictability is not expected or demanded. The paradigm of such technologies is molecular biology.

Enablement can be inferred by analogy from work performed in closely related systems having closely related functions or activities. See In re Bundy, 209 U.S.P.Q. 48, 51-52 (C.C.P.A. 1981) (ruling that appellant's disclosure was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possessed activity similar to known E-type prostaglandins). This same type of reasoning by analogy is appropriate in these circumstances, because of the conserved structure and function of the domains used to construct the chimeric proteins of the present invention. It is also well known that structure and functions of protein domains are conserved when produced after random gene fragmentation and recombination in gene shuffling. This is a general property of protein chemistry and is frequently used to construct chimeric proteins by rational assembly of specific functional domains, as well as by other techniques such as gene shuffling. The results referred to above, particularly those shown in Figure 4 and Table I, would be interpreted by one of ordinary skill in the art as meaning that such construction was likely to be successful.

The specification need not recite details of the claimed invention where one of ordinary skill in the art would consider these details obvious or well known in the art. In re Skirvan, 166 U.S.P.Q. 85 (C.C.P.A. 1970). The quantity of detail permitted to be omitted can be substantial when the state of the art is such that the detail could be readily supplied by one of ordinary skill in the art. This is true even if no working examples are furnished. In re Strahilevitz, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (immunochemistry). It then follows that the presence of working examples, as provided in the specification of the present application, strengthens the case for enablement. These working examples include examples of chimeric isoprenoid synthases, including such chimeric synthases that produce two distinct products.

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." In re Wright, 27 U.S.P.Q. 2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. In re Buchner, 18 U.S.P.Q. 2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). An exact correlation is not required, only a reasonable correlation. As detailed further below, this reasonable correlation is provided by the structure-activity relationships and the actual preparation of a chimeric isoprenoid synthase detailed in the present specification. This does not require recitation of the specific products produced by the chimeric isoprenoid synthase; that goes far beyond the requirements of both statute and case law. This is true even though one of ordinary skill in the art would be able, to a substantial degree of certainty, to predict those products from the information provided in the specification and general knowledge in the areas of isoprenoid chemistry, protein chemistry, and nucleic acid expression.

Even should considerable experimentation be required, this does not constitute "undue experimentation" if the experimentation required is routine and the worker is given sufficient guidance. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). Thus, the amount of experimentation that *might* be required does not give rise to a conclusion of lack of enablement. Moreover, complete reproducibility is not required to find enablement. Johns Hopkins University v. CellPro, Inc., 47 U.S.P.Q. 2d 1705 (Fed. Cir. 1998). In fact, under the holding of Johns Hopkins University, the fact that some attempts at reproducing the claimed invention fail does not lead to a conclusion of undue experimentation. In Johns Hopkins University, the invention concerned monoclonal antibodies, and attempts to reproduce the claimed invention did not uniformly result in success. The Federal Circuit held that this did not constitute undue experimentation, because a certain amount of experimentation was inherent in the Kohler-Milstein process for producing monoclonal antibodies, and a certain degree of irreproducibility was expected. Id. This decision is particularly relevant for the present application in view of the existence of a working example of a multifunctional enzyme producing two different products, namely CH13. The existence of such a working example in this technology is strongly supportive of enablement, notwithstanding the fact that a certain degree of experimentation might be necessary to reproduce this example. This degree of experimentation is to be expected in a complex technology such as recombinant DNA technology and does not support a conclusion of lack of enablement.

How a teaching is set forth, by specific example or broad terminology, is not important. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). Claims are not rejected as broader than the enabling disclosure under the first paragraph of 35 U.S.C. § 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious. In re Skrivan, 166 U.S.P.Q. 85, 88 (C.C.P.A. 1970). Here, the conditions for generation of recombinant isoprenoid synthases would be understood by

one of ordinary skill in the art and no further detail would be needed to enable one of ordinary skill in the art to reproduce the invention.

The degree of unpredictability must be considered within the context of the invention and the knowledge of those skilled in the art. Even broad claims can be enabled if the subject matter of the claims is such that the unpredictability of what is actually claimed is minimized. See In re Vaeck, 20 U.S.P.Q. 2d 1438, 1444-45 (Fed. Cir. 1991) (claims directed to expression of chimeric genes in specific genera of cyanobacteria allowable even though claims were not limited to expression of genes encoding particular Bacillus proteins in view of extensive understanding in the prior art of toxicity of Bacillus proteins). The skill of those of ordinary skill in the art clearly encompasses the preparation and use of chimeric proteins such as those recited in the claims at issue, as well as of plant cells and transgenic plants incorporating DNA encoding such chimeric proteins. This is another strong argument for enablement of the claimed invention.

All that is required to provide enablement is that any mode of making and using the invention be recited in the specification. Engel Industries, Inc. v. Lockformer Corp., 20 U.S.P.Q. 2d 1300 (Fed. Cir. 1991). This test is clearly met here by the examples of particular chimeric proteins produced by domain swapping and mutagenesis described in the specification and examples of their use, when this is coupled with the knowledge of one of ordinary skill in the art of the ability to manipulate protein domains. This conclusion is reinforced by the correspondence between exons and domains shown in the specification of the above-identified application.

Moreover, there is no requirement that all compositions within the scope of the claimed methods provide the same degree of efficacy or activity. In re Gardner, 177 U.S.P.Q. 396 (C.C.P.A. 1973); In re Fouche, 169 U.S.P.Q. 429 (C.C.P.A. 1971). The fact that some of these chimeric isoprenoid synthases may have greater enzymatic activity than others does not mean that undue experimentation exists.

As emphasized above, the division of a complex protein into domains provides a way, well understood in the art, to manipulate the structure of such proteins to combine them into a chimeric protein while preserving their function. This is particularly significant with respect to this application, as the domains correspond to exons and thus are likely to be associated with specific regions of the protein that carry out particular portions of the enzymatic reactions.

As is frequently the case in enablement questions, a review of the factors set forth by the Federal Circuit in In re Wands, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), is useful. The Wands factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented: (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. Id.

A review of these factors indicates that enablement is present. The conclusion is that a rejection under the first paragraph of 35 U.S.C. § 112 should be withdrawn.

Regarding Factor (1), the quantity of experimentation required is not excessive in view of the subject matter. The protein domains, and the corresponding nucleic acid sequences, involved in the construction of nucleotide sequences encoding the chimeric isoprenoid synthases of the present invention are described in detail. Methods of producing nucleic acid sequences encoding such chimeric isoprenoid synthases are also described in detail, including suitable restriction endonuclease fragments. The same is true of proteins encoded by these nucleotide sequences; in any event, once the nucleic acid sequence encoding the protein is specified, the amino acid sequence of the protein resulting from eventual translation of the nucleic acid sequences are completely determined through the standard genetic code and is immediately known. Additionally, the invariant amino acid residues required for the catalysis of particular enzymatic reactions by these proteins are described. The detail in the specification reduces the

degree of experimentation required, as no experimentation is required to select appropriate nucleic acid sequences or produce nucleic acid constructs encoding the chimeric isoprenoid synthases.

These teachings require little experimentation to be carried out by one of ordinary skill in the art. In particular, one of ordinary skill in the art would be able to construct nucleotide sequences corresponding to any protein sequence within the scope of the claims by the use of the genetic code coupled with standard techniques of polynucleotide synthesis, such as solid-phase nucleotide synthesis. Alternatively, the appropriate nucleic acid constructs could be assembled by using restriction endonuclease cleavage fragments, as described in the specification. Although the correspondence of exons and functional domains and the use of restriction enzymes to achieve domain swapping provides one route to the nucleotide sequences of the present invention that encode chimeric isoprenoid synthases, that is not the only possible route to such nucleotide sequences. Other routes, involving random fragmentation and recombination and not necessarily relying upon prediction of functional domain structure, are also available. These routes are described generally as "gene shuffling."

Regarding Factor (2), the amount of direction or guidance presented in the specification is substantial. This direction or guidance includes the information, as described above, with respect to the methods for the preparation of nucleic acids encoding chimeric isoprenoid synthase proteins and the resulting proteins produced by translation of the nucleic acid constructs. Moreover, as indicated above, a successful working example is present and invariant residues in isoprenoid synthase proteins are identified; these invariant residues are identified with specific partial reactions carried out in the course of the isoprenoid synthase reaction. The exact methods used are described in detail.

Regarding Factor (3), the nature of the invention is such that undue experimentation is not present, when the scope of the claimed invention is taken into account. The claimed invention, from the standpoint of enablement, is of a relatively

restricted scope. Moreover, the functional language recited in all claims subject to this rejection, as amended, must be taken into account in evaluating the existence of enablement. In re Halleck, 164 U.S.P.Q. 647 (C.C.P.A. 1970). These claims all recite that the protein encoded by the nucleic acid possesses isoprenoid synthase activity such that the chimeric isoprenoid synthase polypeptide encoded by the DNA catalyzes the production of an isoprenoid reaction product that is not produced in the absence of the second isoprenoid synthase polypeptide. This language removes non-functional proteins, and, thus, nucleotide sequences encoding non-functional proteins, from the scope of the claims. These are not claims for which a degree of extrapolation is required such that the extrapolation would lead to a conclusion of undue experimentation based on the burden placed on one of ordinary skill in the art to achieve enablement within the scope of the claimed invention. Compare In re Strahilevitz, 212 U.S.P.Q. 561 (C.C.P.A. 1982) (enablement found even though no working examples present) with In re Fisher, 166 U.S.P.Q. 18 (C.C.P.A. 1970) (no enablement for claims to an ACTH preparation having a potency of at least 1 international unit/mg, with no upper limit, when specification disclosed preparation of ACTH of potency between 1.11 and 2.30 international units/mg). Here, the scope of the protection sought is relatively circumscribed and the degree of experimentation required is minimal. The degree of experimentation required is minimized by the functional language that excludes non-functional proteins and thus nucleotide sequences encoding non-functional proteins.

Regarding Factor (4), the state of the prior art does not suggest an exceptional degree of unpredictability with respect to the activity of chimeric isoprenoid synthase activity. Although considerations relating to folding of such chimeric proteins do exist, there is sufficient secondary and tertiary structure retained on a domain-by-domain basis to make a reasonable prediction about the structure and activity of the chimeric isoprenoid synthases that are incorporated into the host cells or transgenic plants of the present invention. The degree of unpredictability is further reduced by the functional limitations of these claims. Additionally, the degree of unpredictability is even further reduced by the correspondence between exons and domains referred to above, providing one of ordinary skill in the art with a high degree of confidence that the

construction of the chimeric proteins would be successful inasmuch as the domains corresponding to regions of the protein carrying out specific steps in the reaction catalyzed by the synthase enzymes.

Regarding Factor (5), the relative skill of those in the art is extremely high. This invention is directed to biochemists, microbiologists, and cell biologists, typically with a Ph.D. or other advanced degree in the relevant discipline.

Regarding Factor (6), the predictability or unpredictability of the art was discussed above. As indicated, the degree of unpredictability in the folding and, thus, the activity, of chimeric isoprenoid synthases is reduced by the existence of domains in these proteins with a largely self-contained structure. These domains are largely congruent with the exons in the naturally-occurring genes encoding for these synthases, and with regions of the protein carrying out specific steps in the reaction catalyzed by the synthase enzymes. There is no further unpredictability introduced by the transition between protein sequences and nucleotide sequences that encode the proteins. In particular, there is no evidence whatsoever to suggest that any possible sequence or arrangement of codons that encodes a polypeptide within the scope of the claim would not be functional in transcription.

Regarding Factor (7), the breadth of the claims does not argue for lack of enablement. The claims contain sufficient structure that one of ordinary skill in the art could predict the activity of these chimeric isoprenoid synthases, and undue experimentation would not be required. This is particularly true because of the correspondence between domains and exons referred to above. The structure recited in the claims includes the invariant residues described above. Additionally, the functional language of the claims requiring the presence of protein molecules possessing isoprenoid synthase activity must be considered in evaluating the breadth of the claims. In re Halleck, 164 U.S.P.Q. at 647.

In fact, the Federal Circuit itself, in Wands, found that enablement existed and that undue experimentation was not present. It held that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 U.S.P.Q. 2d at 1404. Wands involved monoclonal antibodies produced by hybridomas. The monoclonal antibodies had to have a certain degree of affinity toward their corresponding antigen. Of 143 hybridomas produced, only 9 were screened further, and of those 9, only four were found to fall within the scope of the claimed invention. This was sufficient to find enablement in the technology under consideration. The fact that some isoprenoid synthases encoded by polynucleotides within the scope of the claims might not have optimal catalytic activity or specificity for a particular isoprenoid synthase substrate does not suggest that the working examples do not yield enablement of the claimed invention. In any event, there is no evidence that suggests to one of ordinary skill in the art that any isoprenoid synthase encoded by any polynucleotide within the scope of the claims would be non-functional or would not have the desired catalytic activity. This evidence strongly indicates that the amount of experimentation required to reproduce the claimed subject matter would be routine and not undue.

As long as the specification discloses at least one method for making and using the claimed invention that bears a "reasonable correlation" to the entire scope of the claimed invention, the enablement requirement of the first paragraph of 35 U.S.C. § 112 is satisfied. In re Fisher, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). That test is met here in view of the teachings of the specification, including a working example of a chimeric isoprenoid synthase that is capable of catalyzing the synthesis of both 5-epi-aristolochene and vetispiradiene.

The situation here is analogous to that in Wands. The claims are of such a scope that one of ordinary skill in the art could use the claimed invention with a reasonable probability of success. There is no requirement that all isoprenoid synthases encoded by polynucleotides within the scope of the claims of the present invention have

the same degree of catalytic activity or specificity, but there is sufficient evidence that at least a significant proportion of them have the required activity.

With respect to the comments that, because Applicant has not taught what products one could expect from the myriad of possible combinations of the broadly claimed chimeric isoprenoid synthases, Applicant has not taught how to make and use the invention as broadly claimed, this does not support a conclusion of lack of enablement. As elucidated above, the claims are not directed to the products or even a method for producing products. As long as one of ordinary skill in the art could use the nucleic acids for generation of isoprenoids, that would be sufficient to satisfy the requirements of enablement under the first paragraph of 35 U.S.C. § 112. The identification of the specific combination of isoprenoids is not required for enablement here. The specification clearly provides sufficient information for one of ordinary skill in the art to make and use the claimed nucleic acid molecules and host cells incorporating them. The "effect" of the claimed invention is the generation of isoprenoids by the synthase enzymes encoded by these nucleic acid molecules. There is no need to teach the synthesis of "any novel isoprenoid compounds" to establish enablement. That is not the standard.

Accordingly, the Examiner is respectfully requested to withdraw this rejection as applied to the amended claims.

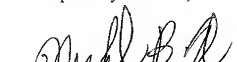
III. CONCLUSION

In conclusion, the amended claims have written description support in the application as filed. These claims are enabled so that one of ordinary skill in the art can make and use the claimed invention without undue experimentation.

Accordingly, prompt allowance of these claims is respectfully requested.

If any outstanding issues remain, the Examiner is respectfully requested to telephone the undersigned at (858) 200-0581.

Respectfully submitted,



Date: December 12, 2007

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